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Aggregation and Toxicology of Titanium Dioxide Nanoparticles

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In their study of inhalation exposure of titanium dioxide particles, Grassian et al. (2007) presented a transmission electron micrograph (TEM) (their Figure 2A) as an image of "dispersed" TiO_2 nanoparticles. Yet, the TiO_2 nanoparticles in this TEM do not appear to be dispersed. There is clear evidence of self-organization of the nanoparticles into distinct assemblages, separated by relatively large regions devoid of any particle. This spatial pattern, very unlikely to occur randomly, is even more apparent when Grassian et al.'s TEM is contrast-enhanced, sharpened, and thresholded (Figure 1A) to eliminate the initial grainy background. With this image, one can demonstrate quantitatively the extent of clustering by calculating the radial distribution function (Torquato 2002), defined as the probability of finding a nanoparticle, in any direction, at various distances away from the center of a given nanoparticle. We compared the values obtained for this function with those associated with an image in which the same nanoparticles have been artificially dispersed (with image processing software). In the dispersed case (Figure 1B), the probability of finding a black pixel drops precipitously when the distance exceeds the apparent radius of nanoparticles, and then stays close to zero thereafter. In the "original" case (Grassian et al.'s Figure 2A), there is also a drop, but the radial distribution function never gets to zero. It progressively increases again as the radial distance increases. This quantitative difference between the curves in Figure 1B leads to the conclusion that the nanoparticles in Figure 1A are clustered.

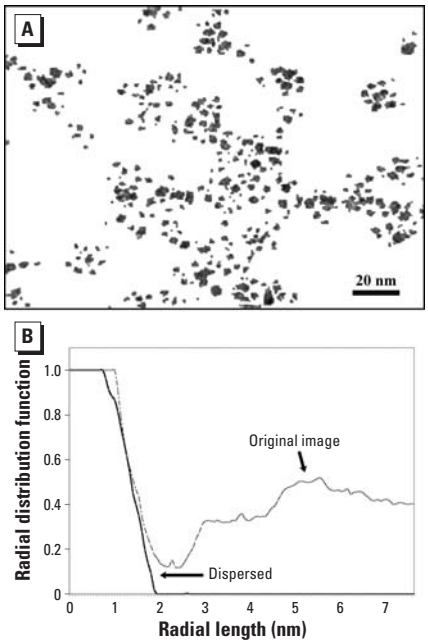

Figure 1. (*A*) Contrast-enhanced, sharpened, and segmented version of a TEM of a TiO_2 nanoparticle suspension (modified from Grassian et al. 2007). (*B*) Radial distribution function versus radial distance for a representative point in a nanoparticle in (*A*); the dashed line indicates values for the "original image" [Figure 2A from Grassian et al. (2007)] and the solid line represents a similar point in an image where the nanoparticles are artificially dispersed.

However, this conclusion is intriguing in itself. Indeed, before obtaining their TEM, Grassian et al. (2007) suspended the TiO_2 nanoparticles in methanol and sonicated the suspension for an unspecified, but presumably appreciable "period of time." Given this strongly dispersive treatment, it is remarkable that aggregation still occurred to the extent it did. This observation suggests that the 2- to 5-nm size of the primary TiO_2 "nano"-particles may be somewhat irrelevant to environmental and toxicologic concerns because in nature, under conditions far more conducive to aggregation than those imposed by Grassian et al. (2007), nanoparticles may never be found alone, but are part of significantly larger-sized aggregates. In a recent study, French et al. (French RA, Jacobson AR, Kim B, Isley SL, Penn RL, Baveye PC, unpublished data) observed that in aqueous suspensions under a range of environmentally relevant conditions of pH and ionic strength, TiO_2 nanoparticles form aggregates of several hundred nanometers to several micrometers in diameter within minutes.

This aggregation may have toxicologic implications. In any given system (e.g., aerosols), it is possible that even a slight change in pH or ionic strength may cause TiO_2 nanoparticles to cluster differently, and therefore to have very dissimilar biological activity. In general, this might explain mixed results found in the literature on the toxicity of TiO_2 nanoparticles to environmentally relevant species. Until now, these inconclusive results have been explained (Oberdörster et al. 2005) by arguing that the high biological activity of TiO_2 nanoparticles, caused by their large specific surface area, creates a high potential for inflammatory, pro-oxidant, and antioxidant activity. Yet, conflicting observations may perhaps be imputable instead to compounding factors due to nanoparticle aggregation, which so far has not been given serious consideration.

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Titanium Dioxide Nanoparticles: Grassian et al. Respond

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Baveye and Laba have further analyzed the transmission electron micrograph (TEM) image shown in Figure 2A of our article (Grassian et al. (2007b) to quantitatively determine the extent of titanium dioxide nanoparticle clustering in the image by calculating the radial distribution function. The main point of doing this calculation was to demonstrate that TiO_2 nanoparticle aggregates will not completely deaggregate even when subjected to harsh conditions.

We completely agree with the statement of Baveye and Laba that "aggregation may have toxicologic implications." We disagree with their suggestion that "nanoparticle aggregation … so far has not been given serious consideration." There is growing consensus that nanoparticle aggregation is an important factor in understanding the health implications of nanoparticles. This has been described by researchers working in the area of nanoparticle toxicity (Balbus et al. 2007; Powers et al. 2006), as well as by us. In addition to Grassian et al. (2007b), we refer to another study in which we further investigated TiO_2 nanoparticle aggregation in inhalation and instillation studies (Grassian et al. 2007a). In that study we demonstrated that the size and nature of

nanoparticle aggregates are important factors in evaluating their toxicity, and we suggested that the natural behavior of these particles and the manner in which people are exposed are critical factors in determining risk. If the nanoparticles do not deaggregate when inhaled, then the aggregation size and nature may be significant physicochemical properties in the toxicity of nanoparticles.

Moreover, combining extensive physicochemical characterization studies of nanoparticles with evaluation of their toxicity, as we have done (Grassian et al. (2007a, 2007b), will foster greater understanding of the environmental health impacts of nanotechnology.

V.H.G. is paid a consulting fee as a member of the science advisory board of Nanoscale Materials Inc. (Manhattan, KS) and owns stock shares in that company. In addition, she is a paid member of the scientific advisory board of Northern Nanotechnologies, Inc. (Toronto, Ontario, Canada). The remaining authors declare they have no competing financial interests.

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DDT and Breast Cancer

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In a recent article, Cohn et al. (2007) noted an association between increased breast cancer risk and *p,p′*-DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] exposure early in life. Their article should be interpreted with caution, particularly the estimated 5-fold increase in risk for women born after 1931 the authors reported without qualification in the "Abstract"; this value was repeated in the news article by Manuel (2007). Cohn et al. (2007) evaluated three DDT congeners—that is, *p,p′*-DDT, *o,p′*-DDT [1,1,1-trichloro-2(*p*-chlorophenyl)-2-(*o*-chlorophenyl)ethane], and *p,p′*-DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene]—by various categories of year of birth, yet they found no significantly increased risk estimates for any of the three DDT congeners in multiple comparisons that were not adjusted for the other DDT-related chemicals either in all women or in women born after 1931. The estimated 5-fold increase in risk for the upper tertile of *p,p′*-DDT serum levels was only observed in subgroup analyses that were both restricted to women born after 1931 and adjusted for serum level of *o,p′*-DDT. The impact of the adjustment for *o,p′*-DDT on the risk estimate for *p,p′*-DDT is remarkable in view of the low *o,p′*-DDT levels observed (35% were below the limit of detection). A significant inverse association between *o,p′*-DDT level and breast cancer risk, which was interpreted by Cohn et al. in terms of length of time since DDT exposure, became stronger after adjustment for *p,p′*-DDT levels; presumably this does not indicate a protective effect of recent DDT exposure.

In view of the absence of evidence for an association between *p,p′*-DDE levels and breast cancer risk (Lopez-Cervantes et al. 2004), it seems unlikely that DDT exposure increases the risk of breast cancer. Nonetheless, if the effect of DDT exposure early in life on breast cancer risk is large [a possibility suggested by Cohn et al. (2007)], then the decreasing birth cohort trend in breast cancer risk that has been observed for U.S. baby boomers is even more remarkable (Chu et al. 1999; Tarone 2006, 2007; Tarone and Chu 2000). Women born after 1945 would have been exposed to DDT for each of the first 13 years of life, with increasing exposure through the late 1960s (Wolff et al. 2005), but the birth cohort risk of breast cancer showed a marked decrease among U.S. women for over two decades after 1945. DDT exposure would join a list of other breast cancer risk factors predicting increasing breast cancer risk in baby boomers (Tarone 2006); yet the birth cohort risk of breast cancer decreased for women born after 1945. That the hypothesized association between DDT exposure and breast cancer risk has received far more attention than the paradoxical decreasing risk of breast cancer that has actually occurred among young U.S. women says much about the priorities and focus of environmental epidemiology.

The author declares he has no competing financial interest.

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DDT and Breast Cancer: Cohn et al. Respond

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We thank Tarone for his letter, as it provides an opportunity to elaborate on analytic strategies for the study of DDT associations with breast cancer.

One feature of our study (Cohn et al. 2007)—assessment of exposure in blood samples collected during active DDT use in the 1960s—provided a unique opportunity to examine three DDT-related compounds singly and in combination. The three DDT-related compounds studied represent distinct aspects of exposure. *p,p′*-DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] is the primary ingredient of commercial grade DDT. *p,p′*-DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene], the most persistent DDT-related compound, is a metabolite of *p,p′*-DDT that is both made by humans during active exposure, and also ingested directly from food sources where it can be stored for long periods in fat (Morgan and Roan 1975). *o,p′*-DDT [[1,1,1-trichloro-2(*p*-chlorophenyl)-2-(*o*-chlorophenyl)ethane] is a low-concentration contaminant of commercial DDT that is eliminated by humans most quickly, making it a marker of recent exposure (Morgan and Roan 1975). Therefore, absolute and relative DDT/DDE isomer levels may represent different windows of exposure (Wolff et al. 2007).

Unlike our investigation, most other breast cancer studies were conducted long after active use of DDT ceased. Thus the preponderance (> 95%) of their exposure was only *p,p′*-DDE [see our Figure 1 and Table 1 (Cohn et al. 2007)]. Hence, our study provides new information. An additional

dimension is that these compounds have been shown to have distinctly different endocrine activity (Kelce et al. 1995), suggesting potential for differential effects on human outcomes. Therefore, we disagree with Tarone's assertion that the lack of an association between *p,p′*-DDE and breast cancer risk in young women refutes a role for *p,p′*-DDT exposure. The timing, origin, and functional activity may differ for each compound.

Concurrent measurements of *p,p′*-DDT, *p,p′*-DDE, and *o,p′*-DDT allow evaluation of potential differences in the effects of these compounds. Other studies have also observed differing associations with cancer risk for *p,p′*-DDT and its metabolite, *p,p′*-DDE. McGlynn et al. (2006) reported that the *p,p′*-DDT association with risk of liver cancer was enhanced when *p,p′*-DDE was low. We also reported that a higher proportion of *p,p′*-DDT to *p,p′*-DDE in maternal serum samples was associated with longer time to pregnancy in their daughters 30 years after exposure *in utero* (Cohn et al. 2003). In another other breast cancer study, Romieu et al. (2000) showed a significant effect for *p,p′*-DDE—after adjustment for *p,p′*-DDT—for predicting breast cancer, particularly in postmenopausal women. We believe that simultaneous adjustment for DDT-related compounds is a strength of our study.

Tarone suggests that subgroup analyses weaken the results of our article (Cohn et al. 2007). However, we pointed out in our article that subgroup analyses, by birth cohort, were planned *a priori* and were a primary objective of our study. In this setting, subgroup analyses are a strength that enabled us to examine whether age at DDT exposure may be of importance in human breast cancer.

The trends in breast cancer incidence in young women previously presented by Tarone in Table 1 of his article (Tarone 2006) do not refute a possible effect of DDT exposure in childhood. Successive birth cohorts of women diagnosed at 20–39 years of age between 1975 and 2002 (Table 1; Tarone 2006) experienced decreasing DDT exposure in childhood (birth years 1941–1982) because DDT use began in 1945, peaked in 1959, and was banned in 1972 in the United States (U.S. Environmental Protection Agency 1975). Successive birth cohorts of women diagnosed at 40–49 years of age between 1990 and 2002 (Table 1 in Tarone 2006) were all exposed to DDT in childhood (birth years 1941–1962); therefore, breast cancer trends for these birth cohorts are not informative for investigating effects of DDT exposure in childhood. Further, we agree with Weiss (2007) that trends in invasive disease and mortality cannot be interpreted without consideration of the rising incidence of *in situ* disease and its successful treatment, which would reduce incidence of invasive disease and mortality.

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Comments on "The Sweet Scent on Baby's Breath?"

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The stated mission of *Environmental Health Perspectives* (*EHP*) is

> to serve as a forum for the discussion of the interrelationships between the environment and human health by publishing in a balanced and objective manner the best peer-reviewed research and most current and credible news of the field. (EHP 2008)

We would like to focus on the part of your mission statement, regarding "a balanced and objective manner." For the third time in about as many years, we find ourselves writing to *EHP* to correct inaccuracies in its reporting of the state of the science regarding fragrance ingredients and our understanding of their fate and effects in the environment and human health.

Your news item "The Sweet Scent on Baby's Breath?" (Potera 2007) is yet another example of information conveyed by your journal in a manner that is neither balanced nor objective. For example, you quote the work of Luckenbach and Epel (2005), yet omit the clarifications from the Research Institute for Fragrance Materials (RIFM) that *EHP* published in a follow-up letter to the editor (Salvito 2005).

You continue to allow reiteration of the inaccurate statement that there is little known about the polycyclic musks, when in fact a robust body of scientific studies published in a number of peer-reviewed journals are in fact available, and have been used to support a thorough evaluation in Europe of the risks of these ingredients to human health and environment.

6-Acetyl-1,1,2,4,47-hexamethyltetraline (AHTN) and hexahydro-hexamethyl-cyclopenta (γ)-2-benzopyran (HHCB) have been assessed by the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP 2002a, 2002b) of the European Union and were determined to be safe to human health for their use in cosmetic products. This was noted by Salvito (2005) in his response to the work of Luckenbach and Epel (2005). These ingredients have also been evaluated by the European Chemicals Bureau (ECB) for determination of their environmental hazards [persistence, bioaccumulation, and toxicity (PBT)], and the ECB has determined that these materials are not PBTs (European Chemical Bureau 2004). In addition, the SCCNFP issued favorable opinions on both AHTN and HHCB, finding them safe for use in cosmetic products (SCCNFP 2002a, 2002b). Further, there have been > 40 publications in peer-reviewed scientific journals pertaining to the human health and environmental safety of polycyclic musks (references available upon request).

As a peer-reviewed journal whose stated mission is to present the best science in an objective manner, we are disappointed with your continued lack of objectivity and inability to collect the necessary information to present a true perspective of the science. It would appear that your news staff needs to perform more thorough research in preparing their reports and that your peer-review process may be incomplete.

The RIFM, a nonprofit organization whose research is governed by an independent

expert panel, was established to provide the research and testing necessary to assure the safety of ingredients used in the creation of fragrances. The RIFM has been in existence for > 40 years and has well-established relationships with academia; it is also well known among many regulatory agencies around the world for publishing its work in the peer-reviewed literature. Our organization, as well as others from our industry, are listed on the U.S. Environmental Protection Agency's website under related links (U.S. EPA 2007).

The authors are employed by the Research Institute for Fragrance Materials, which publishes its work in the peer-reviewed literature under the guidance of an independent scientific panel and receives support from the private sector.

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Editor's note: Forum articles are short and cannot be all-inclusive of a topic. "The Sweet Scent on Baby's Breath?"[Environ Health Perspect 115:A491 (2007)] focused on the presence of polycyclic musks in breast milk in the United States, which had never been measured before the study by Kannan and colleagues [Environ Sci Technol 41(11):3815–3820 (2007)]. That said, Smith and Salvito are correct that comment from an industry source should have been included in this article.

Both researchers interviewed for this article [Environ Health Perspect 115:A491 (2007)] expressed concern about the impact of long-term bioaccumulation of polycyclic musks, as well as the lack of full understanding thereof. This concern is shared by others in the field; for example, the most recent Lake Michigan Lakewide Management Plan *(http://www.epa.gov/lakemich/2006/index.html) includes six polycyclic musks—including AHTN and HHCB—on a watch list of pollutants to be reviewed in 2008. As researchers look at different end points (such as efflux transporters) or sentinel species (such as mussels), new data will continue to emerge that warrant further investigation, as well as reporting.*

The Interaction of Agricultural Pesticides and Marginal Iodine Nutrition Status as a Cause of Autism Spectrum Disorders

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Roberts et al. (2007) recently reported on the results of their investigation into the relationship between agricultural pesticides and autism spectrum disorders (ASD) and found an association between organochlorines and ASD. One possible mechanism for this relationship is through thyroid disruption (Cheek et al. 1999). There is evidence to suggest that iodine deficiency might be associated with some of the increase in the reported prevalence/incidence of autism (Sullivan and Maberly 2004). For pregnant women who have a marginal iodine nutrition status, the disruption of the thyroid due to exposure to organochlorines could induce iodine deficiency and result in negative effects on the brain of the developing fetus. The U.S. iodine nutrition status has declined markedly over the last three decades, with the current iodine nutrition status among pregnant women being marginal (Caldwell et al. 2005; Hollowell et al. 1998). Because of the current iodine status of pregnant women, the Public Health Committee of the American Thyroid Association (2006) has recently recommended that all pregnant and lactating women take daily iodine supplements. It is interesting that the ASD case mothers tended to be older and more likely to be non-Hispanic white and non-Hispanic black than controls, which is consistent with a poorer iodine nutrition status in older women and in non-Hispanics in the United States (Caldwell et al. 2005; Hollowell et al. 1998).

Ensuring adequate iodine nutrition status of women, especially throughout pregnancy, is an extremely important public health goal. Given the negative effects of a number of environmental chemicals on the thyroid (Zoeller and Crofton 2000), it becomes increasingly important to ensure that all women have an adequate iodine intake and that the recommended approach to assuring adequate iodine nutrition is through a comprehensive iodized salt program (International Council for Control of Iodine Deficiency Disorders/United Nations Children's Fund /World Health Organization 2001; Sullivan 2007).

The author is a board member of the International Council for the Control of Iodine Deficiency Disorders.

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Editor's note: In accordance with journal policy, Roberts et al. were asked whether they wanted to respond to this letter, but they chose not to do so.